Barili, F., Freemantle, N., Folliguet, T., Muneretto, C., Bonis, M. D., Czerny, M., Obadia, J. F., Al-Attar, N., Bonaros, N., Kluin, J., Lorusso, R., Punjabi, P., Sadaba, R., Suwalski, P., Benedetto, U., Böning, A., Falk, V., Sousa-Uva, M., Kappetein, P. A., & Menicanti, L. (2017). The flaws in the detail of an observational study on transcatheter aortic valve implantation versus surgical aortic valve replacement in intermediate-risks patients. *European Journal of Cardio-Thoracic Surgery*, *51*(6), 1031-1035. https://doi.org/10.1093/ejcts/ezx058

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10.1093/ejcts/ezx058

**Title page**

# The flaws in the detail of an observational study on TAVI vs SAVR in intermediate-risks patients: evidence-based medicine or market-based medicine?

**Position paper /review** from the Working group on Cardiovascular Surgery, European Society of Cardiology

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**TEXT**

**General consideration**

The development and availability of trans-catheter approach for treating severe aortic valve stenosis (TAVI) has warranted clinical trials and observational studies to evaluate the safety and short/long term outcomes of newly designed prostheses in order to compare them with the gold-standard treatment, the surgical aortic valve replacement (SAVR) [1, 2]. The new treatment has been initially reserved to patients with absolute contraindications to surgery, and subsequently the evidence of safety of the new devices, as well as the matured and expanded experience with this technology, have led to expand indications also to high-risk patients [3, 4]. Nonetheless, technology runs fast and new prostheses are continuously launched on the market, claiming better performances and wider indications and hence requesting new trials [5]. The PARTNER group recently published a comparison between the latest-generation SAPIEN3 TAVI system (Edwards Lifesciences, Irvine, CA, USA) and SAVR in intermediate-risk patients, advocating a significant superiority of the TAVI and suggesting that TAVI might be the preferred treatment method in this risk-class of patients [6]. These favourable results of transcatheter approach in intermediate risk-patients can lead the decision-makers and the scientific community to consider TAVI no more an alternative but the standard of care in a wider population of patients with severe aortic stenosis. The recent Food and Drug Administration (FDA) approval for expanded indications for SAPIEN 3 device based on their data confirms this tendency [7].

Despite the indisputable efforts of the Authors in designing the study [6], methodology reveals major flaws that should be addressed in order to elucidate the actual consistency of the results, otherwise of difficult interpretation and likely leading to misinterpretation. The study is observational and comparison between groups requested preliminary employment of propensity score (PS), a balancing score that identify patients with similar chances of receiving one or the other treatment [8-10], as systematic and significant differences in baseline characteristic invalidate direct comparison and treatment effect ignoring these confounders will be biased [10]. PS analysis is an effective tool that can permit to create a “quasi-randomized” experiment, but it carries well-known intrinsic limitations and pitfalls that can generate incorrect outcomes, such as misspecification of the PS, effects of unknown biases and confounding by

indication [10-14]. Hence, its use does not assure the internal validity of the significance test, and decision-makers and the scientific communities need to be wary of making inference from their results [12]. The study by Thourani and Colleagues shows in its design major PS pitfalls and its results are clearly biased and should be re-analysed [6].

**The assumption of "ignorability" and the effects of propensity score misspecification.**

The first tricky step in PS analysis is the algorithm development, as omission of important confounding factors can lead to biased comparison and estimation of treatment effect. It is hoped that through PS control of the relevant covariates, the treatment will be independent of potential outcomes. This conditional independence assumption is called "ignorability", "unconfoundedness", "selection on observables" and it is always held as an assumption, because we can never be sure after inclusion of which covariates it could be true [15]. In order to assume that treatment assignment is "otherwise ignorable" [10-16], the very first step is the inclusion in the PS algorithm of all known and available confounding factors, as covariates that meet the condition of affecting both treatment assignment and outcome confound the observed relationship between treatment and outcome [10, 16]. The propensity score is seriously degraded when important variables influencing selection have not been collected or considered and misspecification of the propensity score by excluding known confounders has been demonstrated to lead to largely biased results [11].

The study by Thourani and Colleagues has been designed to compare outcomes of an observational study on the latest-generation SAPIEN 3 TAVI System (Edwards Lifesciences, Irvine, CA, USA) with results of the surgical group of the PARTNER 2A trial [5, 6, 17]. The two groups were not homogeneous, as shown in baseline characteristics [6], and the patients' selection bias between the randomized trial and the observational study are even more evident comparing the baseline characteristics of the 2 TAVR groups, hence considering not only the same inclusion/exclusion criteria but also the same treatment option (chi-square p-value <0.0001 for left ventricular ejection fraction and moderate/severe mitral regurgitation, higher STS score in the PARTNER 2A trial TAVR group).

In order to overcome selection bias and obtain conditional unbiased estimates of treatment effect, Thourani and Colleagues planned propensity score stratification before analysing outcomes. Surprisingly, the

comparative analysis of patients' baseline characteristics and baseline variables included in the PS algorithm showed that the most significantly different characteristics between the two groups (left ventricular ejection fraction LVEF, p-value <0.0001; STS score, p-value 0.0002; moderate or severe mitral regurgitation, p-value <0.0001) were omitted in the PS generation, together with other significant factors. These different baseline characteristics are well-known predictors of early and late mortality [18-25] and hence, affecting both treatment assignment and outcomes, are major confounders that should be included in the PS. Their omission violates the "ignorability" assumption and, consequently, the estimation of outcomes is largely biased and uninterpretable.

Moreover, potential confounders not collected in the study are the associated procedures, such as myocardial revascularization. They increase the risk of perioperative mortality and morbidity as widely demonstrated by STS score and EuroSCORE [18-28], and they could represent a major confounder to be included in the PS algorithm if their incidence is different between groups. Nonetheless, although patients with non-complex coronary disease requiring revascularization were considered able to be enrolled if a treatment plan for the coronary disease was agreed before enrolment [5, 6, 17], no information on associated myocardial revascularization in TAVI group has been reported [6, 17]. Luckily, some data on the SAVR group can be derived from the PARTNER 2A trial [5]: a total of 86 of 944 patients (9.1%) had concomitant procedures during surgery and 137 of 944 patients (14.5%) underwent associated coronary artery bypass grafting (CABG) [5]. Summarizing, a proportion ranging between 14.5% and 23.6% had concomitant surgical procedures in the SAVR group of the PARTNER 2A trial, meaning a baseline significant increased risk of mortality and morbidity and a potential major confounder. The claim for a deep analysis on associated procedures in the Thourani's study is also strengthened by the evident significant different proportion of myocardial revascularization in the PARTNER 2A trial (137/994, 14.5% in the SAVR; 39/994, 3.9% in the TAVI group; Chi-square p-value <0.0001) [5]; in a randomized trial that should lead to balanced groups, a preoperatively-planned procedure that affects perioperative outcomes and also reflects a underlying chronic disease independent from the valvular treatment is not randomly distributed between groups. This unbalancing in the randomization process [5] can be only augmented in the Thourani's study where there is no randomization and a patient selection bias is evident.

**Confounding by indication and assessing the performance of the propensity score.**

Confounding by indication is the situation where, although all known confounders have been balanced, allocation to treatment is not otherwise ignorable but instead subject to some latent (unrecognized or unmeasured) process associated with those who are treated. This confounding cannot be measured directly but only tangentially through its effects and hence the effort should be focused on performance analysis of PS [12].

The first useful precaution against unsafe inference from an observational study is to compare it with a known treatment effect and bridge from there to consider further questions. A deeper step in diagnostic should be the evaluation of PS performance through testing the potential heterogeneity of the treatment effect among the PS quintiles. A comparison between two well-balanced groups should lead to a homogeneous treatment effect across quintiles of PS while heterogeneous effects across quintiles should ring alarm bells.

The treatment effect of the observational study by Thourani and Colleagues [6] can be compared to the PARTNER 2A randomized trial [5]. As shown in Figure 1, the relative risk of the main outcome (all-cause death or disabling stroke) significantly differs from the two studies (interaction p-value =0.0001), restraining from drawing strong conclusions in the observational study. Moreover, a deeper analysis of the treatment effect across the PS quintiles shows that the treatment effect is not homogeneous across classes, showing a decreasing pattern through strata and being not significant in the higher quintiles (Figure 2). Only the treatment effect in the fifth quintile is similar to the PARTNER 2A trial effect. It can be hypothesized that in patients with low likelihood of TAVI (lower quintiles of PS) there are important information that PS did not capture and so the match was made with inappropriately low risk individuals, leading to a not otherwise ignorable treatment assignment. [12]

**To adjust or not to adjust, this is another question.**

The concerns also increase in the second part of the study, the time-to-event analyses. The study is based on evidence that groups are different and biased estimated of treatment effects needs to be corrected by balancing the covariates with PS methods [6]. Nonetheless, after employing PS stratification for comparing dichotomic outcomes, Authors unexpectedly avoided any type of adjustment in time-to-event analysis and presented simple unadjusted Kaplan-Meier estimates and curves, making inference on their results [6]. This

appears to be a countersense and the curves are not interpretable, as they are simply a first-step evaluation before adjustment. Stating in results "important differences between TAVR and surgery for each endpoint are observed in the first several months" is inappropriate until data is confirmed by adjusted results. Making inference on unadjusted outcomes derived from biased groups should be avoided [10, 14].

**Is there an outcome missing?**

In the PARTNER 2 SAPIEN 3 observation study, clinical outcomes were reported as defined by Valve Academic Research Consortium (VARC)-2 definitions [6, 29]. The VARC-2 definitions recommend capturing the cause of death with a careful review and, among mortality causes to be reported, all valve-related deaths are included. Valve-related mortality and morbidity represent the main outcomes to evaluate the safety and short/long-term follow-up after valvular treatment, as it is the most specific index of early-late performance. In a comparison between two treatment options for valvular disease considering two homogeneous groups, it can be expected a similar non-cardiovascular and cardiac non-valve-related mortality, while differences in valve-related mortality should be accounted as the treatment effect [30]. Nonetheless, in the PARTNER 2 SAPIEN 3 observation study only all-cause mortality, non-cardiac and cardiac death were reported, while no information on valve-related mortality has been shown. This lack represents another major bias, as it is not possible to differentiate prostheses-related events from prostheses-unrelated deaths, such as those caused by non-embolic myocardial infarction, defined as cardiac but non-valve-related death [29,30]. The unadjusted and adjusted data of valve-related mortality are necessary and no inference on treatment effect of new valvular intervention can be made on non-specific all-cause and cardiac mortality, which are also not adjusted. In the Thourani's study, it is already difficult to justify why 30-day non-cardiac mortality is higher in the surgical group as shown in the Appendix (0.1% and 1.1% in the TAVR and surgical group respectively, Chi-square p-value 0.0152); to summarize that TAVI had better survival based on unadjusted all-cause and cardiac mortality could be a stumble, taking into account also the 14.5% of associated CABG, which means intrinsic higher risk of cardiac but non-valve-related death.

**Conclusions**

As shown, the study on the comparison between SAPIEN3 TAVR and surgical AVR [6] has demonstrated several major methodological pitfalls. Summarizing:

- suboptimal methods in propensity score analysis with evident misspecification of the PS (no adjustment for the most significantly different covariates: LVEF, moderate-severe MR, associated procedures)
- inference on not-adjusted Kaplan-Meier curves, although the Authors correctly claimed for the need of balancing score for adjusting for confounding factors in order to have unbiased estimates of the treatment effect
- evidence of poor fit
- lack of data on valve-related death
-

These methodological flaws invalidate direct comparison between treatments and cannot support Authors' conclusions that TAVI with SAPIEN 3 in intermediate-risk is superior to surgery and might be the preferred treatment alternative to surgery. These unsupported results might be partly related to the sponsored nature of the original trials. Surveys of randomized trials published between 1990 and 2000 raised awareness in the medical community that trials funded by for-profit organizations were more likely to report positive findings than those funded by not-for-profit organizations [31, 34]. Contemporary data has confirmed that incentives surrounding for-profit organizations have the potential to influence clinical trial outcomes [35-37]. Attempts to explain this phenomenon have focused largely on design bias, interpretation bias, data suppression, and differential data quality [35]. Dissemination of clinical trial results is important for clinical practice but appears to be biased in favor of for-profit entities, hence consideration should be given to more extensive promotion of clinical trial results that are funded by not-for-profit organizations. [36]. This should be the gold recommendation in the TAVR vs surgery debate, in order to avoid potential biases not related to medicine but to market.

Adjusting methodologies are formal analysis with precise rules and indications, exactly as for aortic valve surgery/implantation, and cannot be handled at will. What would it happen if physicians handle at own will procedural indications?

**Acknowledgment**

**Sources of funding: None**

**Authors' contributions:**

All Authors participated to conception of the manuscript, drafted and revised the article and gave their final approval to the text.

**Conflict of interest:**

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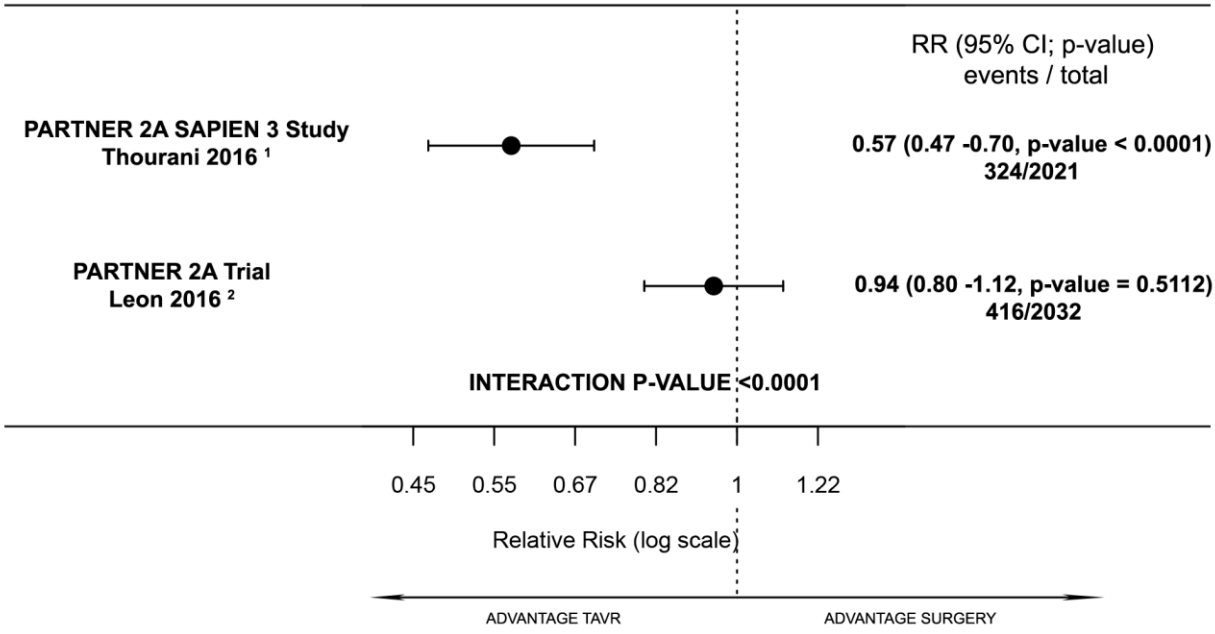
**Figures legend**

Figure 1. Treatment effect of TAVR vs Surgery on all-cause mortality and stroke in PARTNER 2A randomized trial and PARTNER 2A SAPIEN 3 observational study.

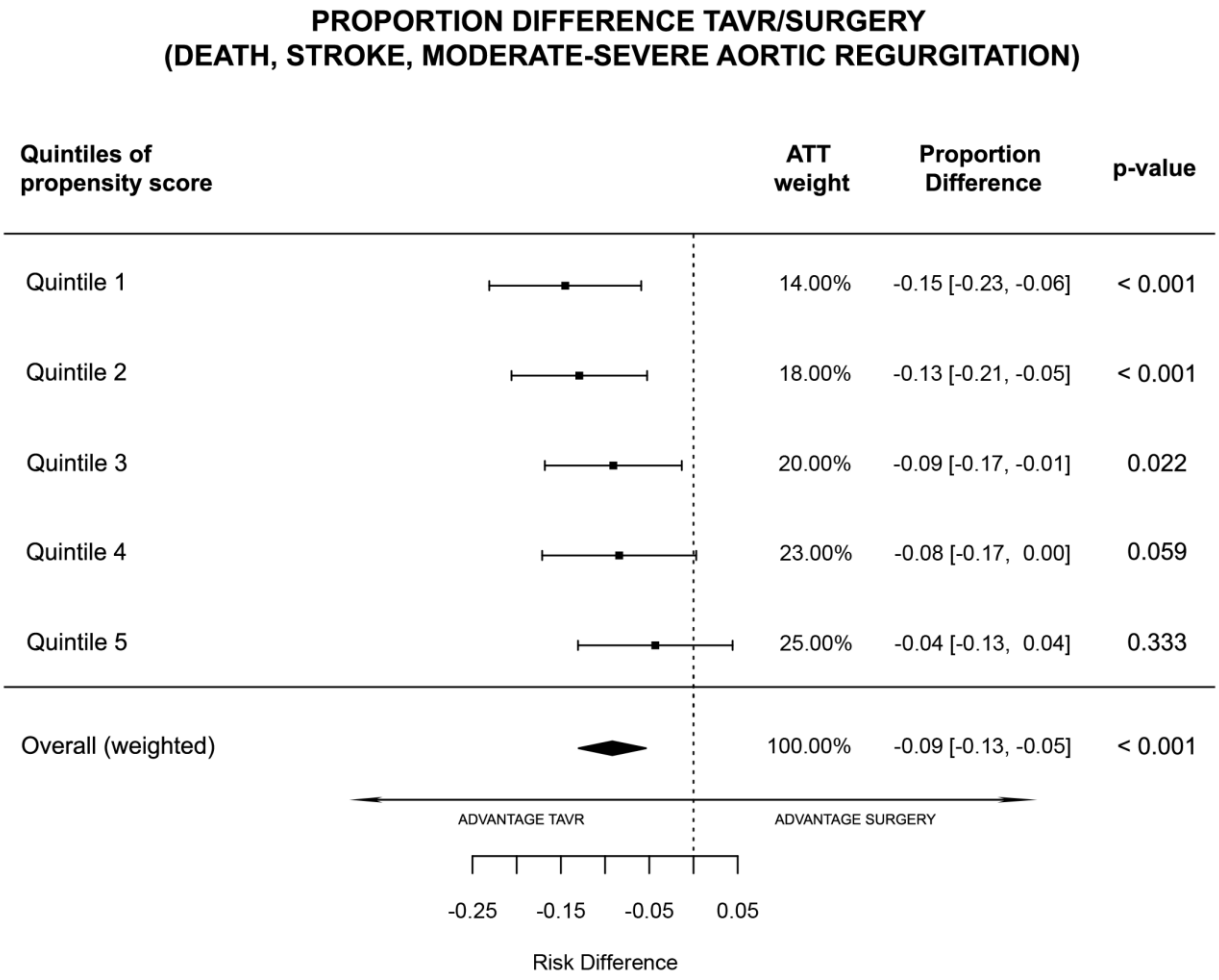
Figure 2. Treatment effect of TAVR vs Surgery on composite outcome (death, stroke and moderate or severe aortic regurgitation at 1 year) across the quintiles of propensity score in the PARTNER 2A SAPIEN 3 observational study.

## RELATIVE RISK TAVR/SURGERY (ALL-CAUSE DEATH OR STROKE)




[1] Lancet 2016; 387: 2218–25
[2] N Engl J Med 2016;374:1609-20

Figure 2


PROPORTION DIFFERENCE TAVR/SURGERY
(DEATH, STROKE, MODERATE-SEVERE AORTIC REGURGITATION)
Quintiles of propensity score
ATT weight
Proportion Difference
p-value
Quintile 1
14.00%
-0.15 [-0.23, -0.06]
< 0.001
Quintile 2
18.00%
-0.13 [-0.21, -0.05]
< 0.001
Quintile 3
20.00%
-0.09 [-0.17, -0.01]
0.022
Quintile 4
23.00%
-0.08 [-0.17, 0.00]
0.059
Quintile 5
25.00%
-0.04 [-0.13, 0.04]
0.333
Overall (weighted)
100.00%
-0.09 [-0.13, -0.05]
< 0.001
ADVANTAGE TAVR
ADVANTAGE SURGERY
-0.25
-0.15
-0.05
0.05
Risk Difference